Toxicology and Potential Health Risk of Chemicals that May Be Encountered by Workers Using Forest Vegetation Management Options

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Introduction

This paper provides summaries for a series of reports on toxicology and potential health risks of chemicals that workers conducting brushing activities may encounter. Principles of toxicology, and assessment of health impacts of some chemical herbicides and chemicals in exhaust emissions of power saws are presented in the series.

Principles of Health Effects Evaluation and Risk Estimation

It is essential that risks associated with the use of any chemical be analyzed objectively. Methods are well established for learning about potential health impacts of chemicals and predicting whether their uses will cause harm. The scientific fields of toxicology, environmental chemistry and epidemiology provide the foundation for such analysis. It is not possible to make such judgements intuitively; individual perceptions of risk rarely correspond to reality. Some trivial risks are seen as enormous and unacceptable, and other very high risks are ignored. Regulatory and administrative decisions about chemical use must be based on valid information about both the utility of the method and its safety.

The biological effects of chemicals follow the natural laws of chemistry, physics and biology; there are no magical chemicals or chemical activities. Obviously it is never possible to know every detail about chemicals or any other component of our lives, but nothing learned about chemical effects is ever found to be outside the orderly structure of nature. All interactions of chemicals with biological systems depend on the physical and chemical natures of both the chemical and the systems that make up living things. The same order applies to behaviour in the environment. It is therefore possible to measure and predict those interactions with sufficient reliability to protect humans and lower species.

The most important example of the order controlling chemical effects is the dose-response relationship. This simple concept is the cornerstone of toxicology and pharmacology. As the dose of a substance increases, so does its effect, and as dose decreases, so does its effect. This principle has been established since the 16th century, and there has been no validated exception. Everyone who has had too much coffee, or observed the effects of alcohol is familiar with the dose-response relationship.

To assess risk (predict the effect of a chemical), we must have two kinds of information. It is first necessary to know what kind of effect a chemical might produce, along with the dose response for those effects. Most of that information can be learned from experimental animals. The other essential information is the dose acquired by humans or other organisms of concern. The dose is some fraction of the amount of chemical contacted on the skin, digestive tract or airway and lungs. That contact is the exposure. A separate section of this report is devoted to estimation of exposure to forestry herbicides.

To assess risks of effects other than cancer, the process is relatively simple once the toxicology is understood. For such effects there is a threshold, a dose below which no effect will occur. If the intake of chemical is much lower than the threshold of effect determined in the laboratory, no adverse effect is expected. For pesticides, this margin of safety must be at least 100 fold, which is much greater than that demanded of household chemicals or other consumer products.

Assessment of cancer risk is more complex for several reasons. The natural background in all species is very high, so small effects are invisible. Cancer cannot be detected until years after it begins, and the effect of the very low doses encountered by workers cannot be measured experimentally. Also, it must be assumed at present that there is no threshold for chemically induced cancer. Assessment of cancer risk becomes a matter of estimating the probability that such an event will occur.

Even though cancer incidence other than lung cancer has remained relatively static for decades

when corrected for our increasing age, about 300 thousand of every million Canadians will have cancer during their lifetime. For regulatory purposes, a hypothetical added risk from some specified activity of one case in a million lifetimes is considered equivalent to zero, and acceptable. Estimating added risk of such a small order requires mathematical modelling of the dose response curve and depends almost entirely on findings in experimental animals, except for a handful of chemicals considered to be known human carcinogens.

Risk as a probability is difficult to grasp; the idea of a one in a million risk might be illustrated as the probability of getting 20 straight heads or tails when flipping coins. The cancer risk due to cosmic radiation associated with flying across Canada and back is about one in a million.

Other irreversible diseases, such as birth defects and miscarriage also have a high natural background in the human population. Birth defects occur in three percent or more of all live births, and about 15% of known pregnancies fail spontaneously. The ability of chemicals to cause these effects can be evaluated in the laboratory. They are dose-responsive and there is a dose level below which no effect will occur.

Pesticide Testing for Registration: Toxicity Environmental Behaviour, and Epidemiology

The registrant of a pesticide must present a broad array of required data to the government before the pesticide can be registered. The results of government's evaluation determine whether the pesticide is registered for use or not. The registration process ensures that the use of the registered product will have no detrimental effect on people and the environment when the product is used in accordance to the label and applicable regulations and standards.

The required information for registration (Table 1) include (i) toxicity data from acute, subacute , subchronic and chronic studies using test organisms (e.g., rabbits, rats, and mice), (ii) fate of the pesticide in the organism including the metabolic conversions and derivatives, excretion, possible storage, and the rates at which these processes take place, (iii) impact of the product on wildlife, fish and invertebrates, and (iv) the environmental residues of the pesticide (e.g., in plants and animals, drinking water, soils) and bioaccumulation.

Epidemiological studies also have a role in the registration process since they can sometimes be used to evaluate possible effects of the product in humans. However, there are some limitations with epidemiological studies. To ensure the reliability of epidemiological evidence a set of criteria are used to evaluate a cause and effect relationship between exposure to a substance and the subsequent development of disease. The following criteria are useful in evaluating the evidence:

a) Strength of Association: Simply put, the bigger the relative risk or the stronger the statistical significance, the greater the likelihood that there is a true cause and effect mechanism at work.
b) Consistency (Reproducibility): It is necessary to compare several studies before a conclusion can be reached since the result from a single study may be a fluke.
c) Dose-response relationship: The amount of illness or change should increase with increasing exposure to the causal agent.
d) Coherence or biological plausibility: Does an apparent relationship fit with other knowledge and does it make sense?
e) Temporal Relationship: Does the presumed cause precede the effect?

Though epidemiological evidence has some problems and not very sensitive, it is sometimes possible to relate exposure to tumour incidence with some modest reliability, usually in the industrial context where work histories may be on record, and where exposures were apparently heavy.

Table 1: Required data for pesticide registration

(a) Toxicity Data
Acute oral toxicity
Acute dermal toxicity
Acute inhalation toxicity
Delayed neurotoxicity in hen (standard test animal)
90 day, rodent
90 day, dog
21 day dermal, rabbit
90 day dermal, rabbit
90 day inhalation, rat
90 day neurotoxicity, hen
Chronic toxicity, two rodent species, two year (may be combined with cancer study)
Oncogenicity (cancer), rat and mouse
Chronic toxicity, dog, one or two year
Teratogenicity (birth defects), rat and rabbit
Reproduction, rat, 2 or 3 generation
Gene mutation (Ames tests and USE OF other microorganisms)
Structural chromosomal alteration
Other genetic toxicity as specified.
(b) Pharmacokinetics and Metabolism*
Dermal absorption
Distribution in the body and duration of residues
Metabolism (chemical change by liver and other organs)
Routes and time course of excretion.
(c) Wildlife, Fish and Invertebrates
Acute and subacute toxicity, small mammals
Acute and subacute and reproduction toxicity, birds
Terrestrial and aquatic invertebrate toxicity and lifecycle
Coldwater and warmwater fish toxicity
Fish early life stage toxicity and life cycle
Toxicity to estuarine and marine fish, mollusks, shrimp, if necessary
Bioaccumulation in aquatic organisms (crustaceans, fish, insects, mollusks).
(d) Environmental Chemistry and Residues
Chemical nature of residues in plants and animals
Residues in all crops on which pesticide is to be used, which could mean 50 to 100 different crops
Residues in meat of livestock species, milk, poultry, eggs, fish and shellfish
Residues in drinking and irrigation water, and residues resulting from use of irrigation water
Dissipation in soil, aquatic sediment, forest soils and litter, under several representative conditions
Accumulation in crops and other media over time.

* Fate of the pesticide in the body, including conversion to derivatives and time courses of various processes

Risks to Workers Associated With Exposure to Emissions from Power Saws

This report is an assessment of the health risks arising from exposure to power saw exhaust during brushing activities. The exhaust of a chain saw or brush saw contains many toxic compounds, including potent mutagens and carcinogens, irritants and central nervous system depressants. Exposure to exhaust components during vegetation management work has not been measured directly. However, measurements taken during logging activities indicate that work in deep brush and quiet air can result in exhaust concentrations that may impair health.

Emissions from two-stroke engines and the nature of their health effects

Two-stroke (chain-saw) engines produce much the same kinds of combustion products as automobiles. In addition, about 30% of the fuel of a typical chain-saw engine emerges unburned in the exhaust. Table 2 lists concentrations of chain saw exhaust components *at the saw*. Several of the substances or groups listed in Table 2 are known to be carcinogenic. Benzene is a confirmed human carcinogen. The chemical 1,3-butadiene is not noted in the table, but is present in two-stroke engine exhaust and is also identified as a known human carcinogen. Several of the polyaromatic hydrocarbons are probable human carcinogens. The hydrocarbons are direct central nervous system depressants, and may be responsible for the nausea reported by fallers and other users of chain saws. Formaldehyde and other aldehydes, and nitrogen and sulfur oxides probably account for most of the irritant quality of exhaust gases. Upon entering the bloodstream, carbon monoxide combines with hemoglobin to inhibit oxygen transport from the lungs to the cells. This may impair physical and mental competence.

Annual use of a single chain saw was roughly estimated by the United States Environmental Protection Agency (USEPA) in the early nineties to produce approximately the same output of volatile organic compounds as 14,400 km of driving current technology passenger cars.

Table 2. Concentrations of chain-saw exhaust components at the saw

Substance	Concentration (mg/m^3)	Relative standard deviation (%)
total hydrocarbons[a]	33 000	23
benzene	1 400	16
total aldehydes	330	20
formaldehyde	120	16
naphthalene	14	84
benzo(a)pyrene	<0.005	
total PAH[b]	75	79
carbon monoxide	66 000	32
nitric oxide (NO)	45	48
other nitrogen oxides (No_x)	50	55

[a] Total hydrocarbons include benzene, PAH, and numerous other straight and branched chain compounds.

[b] Polyaromatic hydrocarbons, including naphthalene and benzo(a)pyrene.

Exposure to exhaust from power saws

A great deal is known about the toxicology of exhaust components. However, this information is only useful in assessment of health risk when the amount reaching the respiratory tract, the exposure, is known. Most gaseous materials that enter the respiratory tract are well absorbed.

For the assessment in this report, the maximum breathing zone concentrations reported for timber fallers is assumed to be the level expected in still air, while cutting brush. A typical lung ventilation rate under hard physical work is about 2.5 m^3/hour. Actual time on the saw in brushing operations is about four hours daily, which would result in about 10 m^3 of contaminated air entering the lungs per work shift. Breathing zone concentrations of several components have been measured during logging in deep snow in a "sparse" pine forest and in a "thick" forest during snow free conditions in Sweden. A survey of operators showed that the worst subjective symptoms of exposure were associated with thick forest, calm weather and deep snow. Table 3 (adapted from Nilsson *et al.*, Am. Indust. Hyg. Assn. J. 48:99, 1987) shows a portion of these data. The wide variation shown is reported as due to differences in wind velocity.

The time-weighted average (TWA) concentration of benzene in the breathing zone was 0.6 mg/m^3. Given the known approximate ratio of 1,3-butadiene to benzene, the estimated concentration of 1,3-butadiene is 0.18 mg/m^3. The current recommendations of the American Council of Government Industrial Hygienists (ACGIH) is an allowable average concentration of 0.3 mg benzene/m^3 and 22 mg 1,3-butadiene/m^3. Exposure to benzo(a)pyrene and other polyaromatic hydrocarbons could not be estimated because of the lack of data.

Table 3. Breathing zone concentrations of chain-saw emissions during logging operations

	Snow free[a]		With snow[a]	
Substance	**Range (mg/m^3)**	**TWA***	**Range (mg/m^3)**	**TWA***
total Hc[b]	7-40	15	3-74	19
benzene	0.3-1.8	0.7	0.1-2.4	0.6
formaldehyde	0.04-0.2	0.08	0.02-0.1	0.08
PAH[c]	0.01-0.04	0.02	0.02-0.04	0.03
CO[d]	24-44	34	10-23	20

[a] Temperature range snow-free -3° to +8°C; with snow -16° to +1°C.

[b] Hydrocarbons.

[c] Polycyclic aromatic hydrocarbons.

[d] Carbon monoxide.

* TWA - time-weighted average.

Estimation of non-cancer or systemic risks

Systemic (non-cancer) effects are reversible and not cumulative unless massive damage occurs, and may be undetectable at low doses. The non-carcinogenic compounds of greatest concern are carbon monoxide and the aldehydes (acrolein and formaldehyde). The significance of hydrocarbons, and nitrogen and sulfur oxides cannot be evaluated at present.

Carbon monoxide (CO)

Carbon monoxide poisoning is reversible, but recovery is slow. Time for half-recovery in a normal atmosphere is about five hours. The upper ranges of breathing zone CO concentration that have been observed are probably sufficient to impair some functions in four hours of working time. American Council of Government Industrial Hygienics (ACGIH) has proposed that an eight-hour TWA of 25 mg/m^3 for CO should not be exceeded. This recommendation falls right into the middle of the range for TWA in the Swedish study summarized in Table 3. A numerical estimate of risk is not possible, but the apparent exposures indicate that breathing zone and blood studies are needed.

Aldehydes, particularly formaldehyde and acrolein

Existing data indicate that exposure to formaldehyde during brushing may reach 0.2 mg/m^3, which will cause upper respiratory irritation and distress. Acrolein is a related compound acting by a similar mechanism.

Estimation of cancer risks

Cancer risk assessment is a process of using existing information to predict a future burden of cancer that a chemical may add to the high normal background that has always existed in the population. A number of assumptions enter into estimation of cancer risk. Perhaps the most important is that animal studies are applicable in estimating human cancer risk. It is also assumed that a given intake of a chemical will carry the same risk whether acquired over a short time or over a lifetime; the total dose acquired is converted to an average daily dose or average respiratory concentration over a 70-year (25 550-day) lifespan. For brushing operations, it is assumed that a typical work history consists of five four-hour days per week actually on the saw, 20 weeks per year, for five years.

Carcinogens act in a dose-related fashion, just as do all chemicals. In the case of substances that cause cancer, the dose governs the frequency of occurrence and the time required for tumours to develop.

Benzene

Benzene is a confirmed human carcinogen causing leukemia. Excess cancer risk over background due to benzene exposure may be as high as 1.2 chances in 1000 for a worker doing brush control work with a chain saw. That is a higher risk than is usually considered acceptable in the industrial context, and higher by 100 fold than the range of estimated added risk generally assumed to be virtually equal to zero (10^{-6}-10^{-5}; 1 in a million to 1 in 100,000).

1,3-butadiene

1,3-butadiene is classified as a known human carcinogen. Compared with benzene, the average dose is less but the currently stated potency is greater, resulting in a net estimate of cancer risk of about two chances per thousand lifetimes at the higher exposure.

Benzo(a)pyrene (BaP) and other PAH

Benzo(a)pyrene is a potent animal carcinogen, and numerous similar substances found in exhaust are also carcinogenic. This is no data on

exposure during vegetation control activity. If levels of these substances in two-stroke exhaust are as high as those from other engines, exposures may be significant. With such uncertainty, an attempt at quantitative estimation of risk is futile.

Conclusion

Workers using chain saws (and brush saws) are exposed to benzene and 1,3-butadiene, confirmed human carcinogens, and polyaromatic hydrocarbons, which are suspect human carcinogens, as well as carbon monoxide and neurotoxic hydrocarbons. Available data suggest that exposures to these substances may reach unacceptable levels under some working conditions. The sum of excess cancer risks, without an estimate for PAH, is estimated to be on the order to 10^{-3} to 10^{-4} (one chance in 1000 to one chance in 10,000, and may be as high as 3×10^{-3}. Carbon monoxide exposures may be sufficient to cause systemic intoxication and impair work performance and safety.

Recommendations

1. Study of breathing zone atmospheres under the various work conditions of manual brushing should be undertaken. Measurements of carbon monoxide exposure should be coupled with sequential blood analyses to determine cumulative impact.
2. A survey of operator experience with ill effects during brush control work should be carried out.
3. Mitigation measures should be explored, even if exposure information is not complete. Possible actions might include specification of minimum air movement during work, directing exhaust away from operators, and producing a benzene-free gasoline. Masks or respirators are not likely to be useful.
4. With more people working in this area, implications of the potential accompanying health risks must be given.

Exposure to and Absorption of Herbicides Used in Forestry

To predict possible harmful effects of herbicides on workers employed in forest vegetation management, two kinds of information are necessary. The toxicology of the herbicide, or its ability to produce injury, including the effects or lack of effects at varying doses must be known. Then, the amount or dose that workers might acquire in the course of their occupation must be determined. Dosage depends on the exposure, which is the amount of herbicide that will contact skin, respiratory tract or digestive tract, and the fraction of that amount that will be absorbed. Deposition of a chemical on clothing or in the environment without body contact is not part of the exposure.

This paper reviews a variety of research studies of worker exposure in forestry and agriculture from which potential worker exposure in forests may be predicted. Many of the available studies used as a base for estimating exposure to the whole range of forestry herbicides have been done with phenoxy and related herbicides. It is appropriate to use surrogate herbicides for worker exposure prediction when application methods are similar, because herbicide exposure is direct and depends little on behaviour of the chemical in the environment. This report discusses occupational exposure of forest workers only, and does not deal with exposure of the general public. There are several reviews that estimate public exposure, which is very low and infrequent, compared to worker contact.

The most important route of exposure for workers is the skin. For almost all methods of application, intake of herbicides through the skin of the hands and forearms is consistently reported to represent most of the total dose. Much of the remaining exposure for applicators using hand-held equipment is on the lower legs. Inhalation of herbicides is minimal with all methods and does not contribute significantly to herbicide exposure. Oral intake occurs almost

exclusively through eating or smoking without washing.

The most accurate method of measuring intake of herbicides is by analysis of urine of exposed workers for several days after application. All of the herbicides used in forest vegetation management in British Columbia are entirely excreted in the urine with little or no change. If the methods of application are similar, data from study of one herbicide is useful in predicting what the exposure of others will be in similar circumstances. The use of absorbent patches on skin and clothing is of some value for assessing relative exposure, as is the use of fluorescent dye in the formulation. The latter method is of great value in demonstrating effectiveness of protective garments, and lapses in technique.

Exposure research has shown that workers and supervisors can control exposure without compromising work output. It is evident that simple precautions in the form of proper clothing, training, working methods, equipment maintenance and response to mishaps bring exposures down to levels that are a small fraction of the upper ranges of exposures that have been commonly measured. The most important part of the work routine is proper use of proper gloves. As much as 90% of dermal exposure is on the hands and forearms. Gloves should be unlined and impermeable, and several pairs should be available so they can be exchanged and washed at the end of the workday. Impermeable leg covering is highly desirable, because during manual application the lower body is subject to considerable exposure from contact with wet foliage, short range drift and hand-carried equipment. All operations should be organized for easy personal and equipment cleanup because immediate wash-off of spilled herbicide sharply diminishes skin absorption.

Exposure of forest workers, such as planters, who enter treated areas after application is minimal. Even an hour after application, removal of herbicides from foliage to the skin is slight, and after 24 hours will be practically zero. Exposure to herbicides or their combustion products as a result of burning of treated vegetation is also not significant. The identity and toxicity of possible combustion products is known. All are common substances for which Workers Compensation Board occupational exposure standards are in place. The limited toxicity of the herbicides and their degradation products and the enormous volume of dilution in smoke of any density that can be tolerated bring even theoretical maximum exposures to minute levels. Efforts to measure herbicides in smoke from treated areas have not been successful.

The daily intakes or doses of herbicide that should be expected as a result of chemical vegetation management activities are tabulated in this paper, with a description of the research. These observations represent a wide range of worker and management care, and show that exposures can be reduced sharply.

The practices necessary to protect workers are simple and do not compromise productivity. This report therefore assumes that future policy will insist on and enforce proper practices. The risk assessments in this report are based on proper practice, not levels that have been acceptable until now, even though those older exposure standards do not impose significant risk.

The following are some recommendations for exposure management:

1. A provisional maximum herbicide intake standard for workers should be established. This report recommends that the standard should initially be 0.02 mg/kg/day for non-motorized ground herbicide applicators and mixer/loaders, which are the functions with the greatest exposure. The same standard can initially be used for all forest herbicides, with evaluation by urine sampling or other measurement of absorbed dose.
2. An advisory body should be established to examine and modify the provisional standard as needed, determine if standards should be applied to other job functions, and define simple work practices that will meet requirements.

3. A series of worker monitoring studies based on urinary sampling should be devised by the advisory body that will show clearly the results of good practices and provide an empirical data base to support the standards. A program of random sampling should also be developed.
4. A program should be established for investigating, analyzing and responding to any herbicide (or other pesticide) related events that might lead to undue exposure of workers or the public. There are such programs elsewhere that can serve as models.
5. Worker training should be evaluated and if necessary modified to aid in meeting the standards.
6. Excellent exposure histories should be rewarded. This report does not attempt to advise how this might be accomplished.
7. Any formal standards should become part of a best management practices.

Risks to Workers Using 2,4-D Formulations

2,4-D has a broader scientific history than any other herbicide, perhaps more extensive than any other pesticide. It was first marketed in 1947, and the knowledge base for health effects is monumental. There are several reasons for the extensive literature. Much of the required re-registration data has been published in the open literature, which is unusual. Because 2,4-D is one of the most widely used pesticides, it has been the subject of prolific academic and government research. As a component of Agent Orange, the dominant social symbol of the Vietnam War, 2,4-D acquired a mystique about health effects that was independent of real information, and much research has been directed at clarifying those perceptions. Because of the attention, a variety of advisory committees and work groups have been assembled to examine and interpret the data.

2,4-D is not readily absorbed across the skin, but several cases have been recorded in which concentrated material on the skin was absorbed sufficiently to cause general effects. There have been a number of suicide attempts, some successful, which have shown an inconsistent pattern of effects other than general gastro-intestinal irritation, which will occur with almost any chemical ingested in such amounts. In a few individuals, intoxicated with a heavy dose of 2,4-D, a pattern of apparent neuromuscular effects in the limbs has appeared. Animal research has failed to demonstrate a similar effect.

Some formulations of 2,4-D are able to cause skin irritation, which is reversible.

2,4-D is very efficiently and completely excreted by humans, without change in the body, other than conversion of esters and amines to the parent 2,4-D acid in the bloodstream.

2,4-D is not a significant reproductive toxicant. At high doses it can cause foetal and maternal toxicity, which may result in delayed or arrested development. In some mouse studies there has been evidence of cleft palate and eye deformities. The NOAEL for these effects is 25 mg/kg/day. Daily doses of 20 mg/kg/day through three generations does not affect fertility or survival, but does have some effect on body weights of pups and dams.

2,4-D is not considered to be mutagen. Mutagenicity assays demonstrate the potential for a chemical to cause genetic damage and are also an indicator of ability to initiate processes that may lead to cancer.

Early cancer studies of 2,4-D were negative, but not adequate for new registration. Subsequent assays under modern protocols showed no effects in mice, and in rats a low incidence of a brain tumour called astrocytoma. Various expert evaluations concluded that the effect was not related to 2,4-D treatment because the tumours that were seen were not consistent with chemically induced tumours of the central nervous system. The question has been resolved

with new assays a much higher dose rates, showing no evidence of any kind of cancer.

There have been a remarkably large number of epidemiology studies attempting to learn if there is a relation between exposure to 2,4-D (or phenoxy herbicides as a class) and human cancer. Findings have been very inconsistent, and are clouded by inability to isolate 2,4-D exposure from the variety of other potential influences, or to reliably define past exposures. In the epidemiology studies there has necessarily been great dependence on recall of practices decades in the past, either by farmers and foresters, or their kin. Review panels, including that convened by USEPA in April, 1993 have consistently concluded that the evidence is at best weakly suggestive and does not warrant change in regulatory policy.

The question of biological plausibility appears to receive little discussion in the arguments about 2,4-D effects on humans. Exposures to workers are very well documented and are consistently found to be in the low micrograms per kilogram per day range. 2,4-D is not genetically active and it is excreted unchanged. It is inactive at all but massive doses with respect to another, nongenetic, mechanism by which some similar compounds may induce cancer. If 2,4-D is carcinogenic, it would have to act by a mechanism not yet observed in the enormous mass of cancer research of the last three decades, and it would have to be more potent than almost any known carcinogen. If that were the case, cancer among 2,4-D users would be as prevalent as lung cancer among smokers, and would be certainly identified.

There is extensive data on exposure of forest workers to 2,4-D, showing that careless work habits increase exposure, and that simple protective clothing and work discipline reduce exposure to very low levels. The primary concern is skin and eye irritation from certain formulations. Concentrated formulation can be absorbed from the skin in sufficient amounts to cause systemic toxicity but immediate cleansing prevents significant absorption

Risk to Workers Using Glyphosate Formulations

(e.g., Vision® Roundup®, Vantage Forestry®, and Forza®)

Glyphosate as the isopropylamine (IPA) salt is the active ingredient in the herbicide Vision®, which is the registered name for forestry use in Canada. It is identical to the agricultural and industrial formulation Roundup®. New forestry registered formulations of glyphosate are Forza® and Vantage Forestry®. They are reported to be similar to Vision®

Vision® and Roundup® formulations contain 41% glyphosate IPA salt, 15% surfactant, and water. A non-ionic surfactant and water are the only inert ingredients in the formulation. Water is the solvent for the glyphosate. The surfactant helps distribute the herbicide over leaf surfaces by reducing surface tension of the water.

The data necessary for registration of glyphosate herbicides has been developed in studies conducted or commissioned by the registrant and is now considered complete by regulatory authorities in Canada and the United States. Only a part of this information has been published in the open literature, which is typical for most pesticides. However, the data have been audited by the regulatory ministries and agencies and have been made available by the registrant to public agencies and other qualified reviewers.

Behaviour of glyphosate in the body: absorption, metabolism, storage in tissues and excretion

Absorption of glyphosate from the digestive tract is inefficient; most ingested glyphosate remains in the intestine and is removed in faeces. Absorption across the skin is also very slow. Laboratory studies of monkeys, *in vitro* studies with human skin and studies of applicators applying glyphosate in the field indicate absorption on the order of one percent over 12-24 hours. Washing with water or soap and water has been found to remove almost all herbicide that reaches the skin.

Virtually all glyphosate absorbed into the circulation is excreted unchanged by the kidneys within a few days. Following intake over extended periods, low concentrations remain briefly in tissues that have high blood circulation, such as the kidney and liver. This is characteristic of water soluble substances. Glyphosate is not detectable in eggs, milk or meat of livestock when the herbicide has been given in the diet.

General toxicology of glyphosate

In all aspects, the toxicity of glyphosate is limited. Acute oral median lethal doses (LD_{50}) in various species of mammals vary between 3500 and 5000 mg/kg. Mice have tolerated dietary concentrations as high as 50,000 parts per million (ppm) for at least 90 days. The only effect was decreased weight. 50,000 ppm is 5% of the entire diet, and in mice represents an oral exposure on the order of 7500 mg/kg/day. Relatively little of the oral intake was absorbed. Rats may be somewhat more sensitive. A dietary concentration of 5,000 ppm caused some increase in lung weight, but without evidence of cell damage.

Glyphosate and its formulations have no specific target in animals that can serve as a basis for systemic or organ based toxicity. Its action in plants is on a specific biochemical pathway for aromatic amino acid synthesis that does not exist in animals.

Dermal toxicity

The only validated incidents of Roundup® toxicity in humans seen in North America have been skin and/or eye irritation. The skin is the most likely site of contact for any herbicide. A chemical on the skin may either pass through to reach other parts of the body, or cause damage at the surface.

In a comparison of the effects of the Roundup® formulation on human skin with effects of a baby shampoo, a dishwashing detergent and an all-purpose cleaner on a large number of volunteers, the herbicide caused little effect. The shampoo and Roundup® were found to be similar in effect to water, and less irritating than the detergent and the cleaner, whether as a single application or after three weeks of repeated applications.

Concentrations of Roundup® up to 10% do not cause skin irritation or allergic sensitization in humans. Five percent Roundup® will cause eye irritation, however.

Reproductive and developmental toxicity, including birth defects

In multigeneration reproduction tests in which male and female rats and their offspring were fed up to 600 ppm glyphosate (about 30 mg/kg/day) in the diet from weaning through reproduction to weaning, no effects were found in any aspect of fertility, reproductive function or development of offspring.

Glyphosate has not produced birth defects in rabbits given 350 mg/kg/day or rats given 3500 mg/kg/day. These doses did produce maternal toxicity, which is the criterion for the upper dosage limit in such studies.

Genetic toxicity (induction of mutations)

Glyphosate has been assayed for mutagenicity in comprehensive microbial and mammalian cell culture tests, in fruit flies and in intact mammals. It did not cause genetic damage or mutation. Glyphosate also does not interfere with repair of DNA.

Concern has been expressed that a genetically active N-nitroso-derivative of glyphosate may be formed in the environment or be present as a contaminant in the formulation. The compound that can theoretically form is N-nitroso glyphosate, which is not carcinogenic, nor does it have appreciable genetic activity. Formation of this derivative after application can only occur in the presence of other specific chemicals. Simulated spills on a prior fertilizer spill, which is a favoured reactant, produce very little conversion. As a trace contaminant, N-nitrosoglyphosate is no longer found in the formulation.

Potential for causing cancer

Canadian, United States and international regulatory authorities have concluded that there is no evidence that glyphosate is able to cause cancer, on the basis of bioassays in two animal species and other characteristics of the herbicide.

Absence of mutagenicity indicates that glyphosate has no ability to interact with genetic material to initiate the process leading to cancer. It has negligible cellular toxicity and does not cause other changes in cells that have been associated with promotion of carcinogenic processes that may have already begun. It is excreted rapidly, unchanged, and is not retained in the body. All of these factors, along with negative direct assays are convincing evidence that glyphosate is not a carcinogen.

Toxicology and behaviour of the Vision® surfactant

The surfactant is a polyethoxylated tallow amine, a type that is common to vast numbers of cosmetics and household products. The surfactant decreases surface tension of water, so water does not stay in large droplets on the waxy surface of leaves. When the water spreads out it allows more contact of the herbicide with the plant.

At very h.gh intakes, the characteristic effect of the surfactant is gastrointestinal erosion, with secondary responses typical of such injury. The surfactant is irritating to rabbit skin and eyes, and causes some allergic sensitization in guinea pig skin. The Roundup® formulation has shown no potential for sensitization. The surfactant does not have genetic activity and does not cause developmental effects. It does not interact biologically or chemically with glyphosate, and is degraded rapidly by microbial activity.

Exposure of forestry workers to glyphosate formulations

Whether measured directly in terms of urinary excretion or indirectly through analogy with other herbicides applied in a similar manner, glyphosate dosage absorbed by forest workers is very low, with safety factors in excess of 5000.

After an application has dried, potential for exposure of workers or others entering a treated area is very low. Glyphosate binds tightly to soil components and does not move appreciably. Once an application has dried on foliage, glyphosate has either been absorbed into the leaves, or bound to their surfaces. In either case, dislodgement through contact with leaves is difficult. In terms of worker safety, the evidence on behaviour of glyphosate indicates clearly that when an application has dried, further exposure is unlikely.

Exposure to glyphosate or its combustion products during a burn on treated land is not a measurable source of exposure. Maximum possible exposures to each combustion product

in the smoke can be estimated. The resulting doses are far below any level that can cause health impact. Attempts to find other herbicides in smoke during burns of treated areas have been unsuccessful.

Conclusions

The toxicity of glyphosate and its formulations is extremely limited. Glyphosate is not carcinogenic, it does not produce reproductive or genetic effects, and doses required to produce non-specific systemic effects are very high.

Workers applying glyphosate or occupying areas recently treated have been shown to absorb only small amounts of the herbicide, that have no toxicological significance. Ingestion of the concentrated formulation can be expected to cause gastrointestinal effects, and exposure of skin or eyes to the concentrate may result in irritation if it is not washed away.

Glyphosate does not move through the soil from the site of application. It binds tightly to vegetation when dried. Exposure by dislodgement from vegetation is unlikely.

Risk to Workers Using Hexazinone Formulations (Pronone®, Velpar® L)

Hexazinone is a broad spectrum soil-active herbicide used for site preparation, conifer release and in nurseries. This herbicide has attracted little scientific interest outside the registration process, but much of the toxicology data developed for registration purposes has been published in the open literature.

The acute toxicity of hexazinone is low, with median lethal doses (LD_{50}) ranging from 800 mg/kg in guinea pigs to over 3400 mg/kg in dogs. Dermal toxicity is very low, indicating poor absorption across the skin. However, specific skin absorption studies have not been done. Hexazinone is irritant to the eyes, but does not produce skin sensitization.

In a standard 90-day subchronic assay, rats consuming a diet containing 5000 ppm hexazinone (about 250 mg/kg/day) were unaffected except for slightly decreased weight gain. There was no effect at 1000 ppm. Dogs given 200 mg hexazinone/kg/day were unaffected except for modest weight loss.

Two-year cancer studies of rats and mice were designed to provide both carcinogenicity data and long term general toxicity data. There was no detectable carcinogenic response, and there were no pathological changes other than benign adenomas found in the livers of mice maintained on a diet containing 10,000 ppm hexazinone.

Male rats fed a dietary concentration of 2500 ppm and females fed 2500 and 1000 ppm weighed less at the end of the study than controls, and there were changes in organ weight. A lifetime no-effect level of 10 mg/kg/day was derived. The dose rate at which no effects could be observed in mice was 35 mg/kg/day. Some liver effects were detectable at the higher dose rates. Hexazinone was found to have no effect on reproduction and did not cause birth defects at doses that can be tolerated by the dams. It was shown to have limited mutagenic potential.

Hexazinone metabolizes (is changed in the body) to several variants of the basic triazine ring, a pattern similar to that of other triazines. Hexazinone and its metabolites are excreted rapidly, without accumulating in any animal species. Small quantities of hexazinone can be found in milk of heavily exposed mammals. However, the use pattern is such that milking animals are not likely to encounter it. Exposure of lactating wild species would not have significant impact on milk or offspring.

Little direct study of human exposure has been done, but studies of exposure of humans to other herbicides provide information useful in estimating hexazinone exposures. One study from Quebec indicates that spot gun use results

in higher exposures than other methods. The Quebec work emphasizes the role of good equipment and work habits in reducing exposure.

Risks associated with use of hexazinone in forestry are slight, limited to eye and skin irritation. If daily intake is on the order of 0.03 mg/kg, which is to be expected of a worker who is moderately careful, the safety factor based on the NOAEL of 10 mg/kg/day will be over 300. There is no calculable carcinogenic or reproductive risk for hexazinone exposure.

Risk to Workers Using Triclopyr Formulations (Release®, or Garlon 4®)

The Release® formulation is the butoxyethyl ester of triclopyr in a kerosene diluent. Triclopyr is poorly absorbed from the skin, and is excreted by humans and most other species rapidly and without change. The principal effect is skin and eye irritation that may occur after prolonged contact. In experimental animals high oral doses over long periods result in limited and reversible kidney and liver effects. Excretion is through the kidney, largely by a system that can be overloaded if presented with excessive amounts of organic acids, including triclopyr. In that case, concentrations in blood and tissues rise, particularly in the kidney, and the liver processes part of the burden.

Because studies have shown that triclopyr is able to affect kidney function at high dose rates, distribution in tissues and excretion have been evaluated in cattle, goats, rats, rabbits and dogs, and excretion has been investigated in humans. It is clear that humans excrete triclopyr very rapidly.

The evidence shows that triclopyr does not have potential to cause cancer or mutation. Reproductive effects occur as delays in development, but only at doses that cause visible maternal toxicity; therefore triclopyr is not considered a reproductive intoxicant.

Other materials in the formulation include the kerosene diluent and 2-butoxyethanol, which remains from the manufacturing process, at a concentration of about 0.3%.

2-butoxyethanol is a common solvent in household cleaning preparations, usually found in such formulations at concentrations between two and three percent. Both substances are of limited toxicity.

Conclusion

A general statement may be made that even with current work practices, exposures to herbicides used in British Columbia forestry do not represent a health threat to forest workers.

Glossary

Acute toxicity – (Short term toxicity) –Acute toxicity is the quality or potential of a substance to cause injury or illness from a single dose or short period of exposure. See **subacute, subchronic and chronic.**

AEL – Acronymn for adverse-effect level.

Adverse-effect level (AEL) – Signs of toxicity that are not accompanied by grossly observable signs. Such symptoms must be detected by invasive methods, external monitoring devices or prolonged systematic observations.

Cancer – A malignant growth of potentially unlimited size that invades local tissues, and may spread to other parts of the body.

Carcinogen – A chemical capable of inducing cancer.

Carcinogenic – Capable of causing cancer.

Chronic toxicity – (Long-term toxicity) – Chronic toxicity is the quality or potential of A substance to cause injury or illness after repeated exposure for a long period of time. Chronic toxicity tests run for a year or more; for rodents the period may extend through the entire life span. A chronic effect persists for months or years and may arise from acute or long term exposure. See **acute, subacute, subchronic.**

Deoxyribonucleic Acid – See **DNA.**

Dose – The amount of a chemical that actually enters the body to be distributed to all of the organs and cells. Distribution to tissues and cells is selective, and depends on the nature of the chemical and characteristics of each kind of cell.

Dose-response relationship – The central idea in toxicology and in pharmacology (which is the science dealing with beneficial effects of therapeutic drugs). As the dose (or concentration) of a chemical increases, the effect increases, and as the dose is lowered, the effect becomes less. This response pattern applies to every interaction between a chemical and a biological system, whether human, fish, bacteria or any other kind of organism or tissue. The dose-response relationship is absolutely essential to judgement of the effect of any chemical.

DNA (Deoxyribonucleic Acid) – The genetic library in each cell that contains all of the instructions for building and operating the body. Each kind of cell contains all of the information for the whole body. Only the information needed for each kind of cell is used by that cell; the rest is repressed. Liver cells do not try to be muscles, and muscles do not try to become brain cells, but they contain all of the information.

Environmental chemistry – The study of the physical, chemical and biological processes that govern behaviour and fate of a chemical such a pesticide after it is used.

Epidemiology – The scientific study of the cause, distribution, and control of epidemics or other disease in a region. In the context of these reports, epidemiology is the study of possible associations between environmental and occupational chemicals and occurrence of diseases. The term "associations" is used in its statistical sense, which means that the relationship cannot demonstrate cause and effect.

Exposure – Amount of a chemical that reaches a surface from which it might be absorbed. The dose is some fraction of the exposure. Exposure does not include material that is on nearby foliage or other surfaces. It is only the material that reaches the skin (by contact), respiratory tract (by inhalation) or digestive tract (by ingestion).

Formulation – A complete pesticide preparation as sold by a manufacturer for practical use. It includes the active ingredient and any necessary adjuvants and solvents. For use, it may or may not require further dilution or mixing with other substances. Formulation can also be defined as the process used by manufacturers in preparing a pesticide for practical use.

Herbicide – A chemical substance or cultured biological organism, used to kill or suppress the growth of plants.

Irritation – A purely local or topical reaction which may include redness, blistering, swelling, burning or itching.

Lethal – Causing death.

Margin of Safety (MOS) – The difference between the estimated dose of a pesticide and the NOAEL. A **MOS** of 100 (estimated dose 100 fold less than the NOAEL) is usually considered to assure that no adverse effects will occur.

Metabolism – the sum total of the biochemical reactions that a chemical undergoes in an organism. The processes include biochemical (enzymatic) reactions in the cells of the body that convert nutrients to energy and structural materials of the body; reactions that change wastes so they can be removed; and reactions that convert foreign substances, such as some pesticides to forms that can be excreted.

MOS – Acronym for margin of safety.

Mutagenic – Capable of producing genetic changes.

Mutagens – Chemicals that are able to induce gene or chromosome damage that is stable and survives cell division to reach the next generation of cells. See **mutation.**

Mutation – Genetic change in DNA of a cell that can be transmitted to the next generation of cells. If in sperm or egg cells, a mutation may be transmitted to offspring. If in somatic (body) cells such as liver, muscle or other organs, a mutation may pass to daughter cells in the organ. The change may have no effect on cell function or it may damage the cell, or even imaginably improve it.

NOAEL – Acronym for **no-observed-adverse-effect level.**

No-observed-adverse-effect level (NOAEL) – The dose rate or concentration at and below which no adverse effects can be detected. (See **threshold;** see **LOAEL.)** If the estimated dose of a herbicide to a worker is very low compared to the **NOAEL** for the most sensitive effect found in the laboratory, no harmful effect is to be expected.

Oncogenic – Able to cause cancer.

Persistence – The duration of measurable concentrations of a pesticide in soil, foliage or other media. (See Half-life.)

Pesticide – Any chemical (or biological product) intended to control or kill pests. Herbicides, insecticides, fungicides are all pesticides. The term is sometimes incorrectly used to mean only insecticide, for example "pesticides and herbicides."

Pharmacokinetic – Relating to the rate and pattern of the absorption, distribution, metabolism and excretion of drugs in an animal.

Registration – The process by which government (e.g., Canadian federal government) authorities determine that a pesticide is suitable for use. Standards of public and worker safety, environmental impact, and usefulness must all be met.

Risk – The probability (likelihood) that some adverse or undesirable effect will take place in the future, as a result of some specified activity. Risk may relate to health, finances or any other kind of undesirable impact. Real risk may be so small that it cannot be distinguished from zero, or so great that it is a certainty. In the context of pesticides, risk is the probability that use of the pesticide will result in some specified harmful effect on workers or the public. Risk assessment is the process of estimating that probability.

Safety Factor – See **Margin of Safety.**

Sensitization – The initial exposure of an organism to specific antigen (foreign protein or chemically altered body protein) resulting in a response of the immune system such that subsequent exposure induces an allergic reaction.

Subacute – Extending over a few days to perhaps a month. This and related terms do not carry defined time periods; consequently there is overlap in the way they are used. See **Acute, subchronic and chronic.**

Subchronic – For experimental studies, relatively long term, but not as long as a chronic study. Typically three to six months. See **acute, subacute, and chronic.**

Threshold – The lowest dose that will produce a given effect. As a practical matter, the threshold is little different from the **NOAEL.**

Tolerance – Lesser than normal sensitivity of an individual to the adverse effect of a chemical. also, the allowable residue of a pesticide on a food or feed crop.

Toxicity – The whole pattern of harmful effects (illness and other undesirable effects) that a chemical can cause. It is a property of the chemical; it does not change.

Toxicology – The group of scientific disciplines that identifies and studies the adverse effects of chemicals on biological systems, whether in the laboratory or in the field.

Titles in this Series

1 Principles of health effects evaluation and risk estimation for chemicals that may be encountered in forest vegetation management

2 Pesticide testing for registration: toxicity, environmental behaviour, and epidemiology

3 Toxicology and potential health risk of chemicals that may be encountered by workers using forest vegetation management options. Part I: Risk to workers associated with exposure to emissions from power saws

4 Toxicology and potential health risk of chemicals that may be encountered by workers using forest vegetation management options. Part II: Exposure to and absorption of herbicides used in forestry

5 Toxicology and potential health risk of chemicals that may be encountered by workers using forest vegetation management options. Part III: Risk to workers using 2,4-D formulations

6 Toxicology and potential health risk of chemicals that may be encountered by workers using forest vegetation management options. Part IV: Risk to workers using glyphosate formulations (e.g., Vision®, Roundup®, Vantage Forestry® and Forza®)

7 Toxicology and potential health risk of chemicals that may be encountered by workers using forest vegetation management options. Part V: Risk to workers using hexazinone formulations (Pronone®, Velpar® L)

8 Toxicology and potential health risk of chemicals that may be encountered by forest vegetation management workers. Part VI: Risk to workers using triclopyr formulations (Release®, or Garlon 4®)

9 Toxicology and potential health risk of chemicals that may be encountered by workers using forest vegetation management options: Summary

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